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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,063	12/26/2001	Luc Desnoyers	P3030R1C6	4326

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,063	DESNOYERS ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/26/01, 9/4/02, 10/14/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/13/02, 6/24/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendments filed 26 December 2001 and 4 September 2002 have been entered. Claims 22 – 27 are under examination.

Priority

35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

The preliminary amendment filed 4 September 2002 indicates that this application is a continuation of 09/931836, which is a continuation of PCT/US00/05601, which claims priority to provisional application 60/130359, filed 21 April 1999. While applicant disclosed the amino acid sequence in said provisional application, no use for the protein was disclosed.

Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because the provisional application filed 21 April 1999 does not meet the requirements of 35 U.S.C. § 112, first paragraph, it is unavailable under 35 U.S.C. § 119(e). The effective priority date of the instant application is considered to be the filing date of the international application PCT/US00/05601, filed 1 March 2000.

The examiner has determined that the asserted utilities, i.e. the positive results in assays 106 (Detection of Polypeptides that Affect Glucose or FFA Uptake in Skeletal Muscle) and 92 (Mouse Kidney Mesangial Cell Proliferation Assay), do not constitute specific and substantial utilities as required under 35 U.S.C. § 101. The reasons for this determination are enumerated below.

Should applicant argue that the provisional application filed 21 April 1999 in fact is an enabling disclosure, applicant must specifically indicate the page and line numbers where PRO4380 was found to test positive in assays 92 and 106, as well as overcome the rejection under 35 U.S.C. § 101 below.

Information Disclosure Statement

The information disclosure statements filed 3 May 2002 and 24 June 2004 have been considered. The database search results demonstrate that applicants are aware of nucleic acids with identity or homology to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the examiner cannot determine if said sequences constitute prior art.

Specification

The disclosure is objected to because of the following informalities:

The title is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The specification includes browser-executable hyperlinks. This objection could be overcome by deleting all occurrences of the text "http://".

Appropriate correction is required.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 – 27 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The polypeptide of the instant application has been isolated because of its similarity to a known protein. There is little doubt that, after complete characterization, this protein may be found to have a specific and substantial credible utility and antibodies which bind said protein may be useful. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is

incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The claims are drawn to antibodies that bind to PRO4380, as well as monoclonal, humanized, and labeled antibodies and fragments of antibodies. The specification asserts that PRO4380 has two specific utilities, as it came up positive in two assays, however neither utility is substantial.

The research data presented in the instant specification indicate that PRO4380 of SEQ ID NO:57 "tested positive as either stimulator[s] or inhibitor[s] of glucose and/or FFA uptake" in an assay using primary rat differentiated skeletal muscle (page 166, Example 37). Based on the results of the assay disclosed in the Example 37 it was asserted that the instant PRO4380 polypeptides "would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial including, for example, diabetes or hyper- or hypo-insulinemia" (page 166, lines 17 - 19). However, based on the information supplied in the instant disclosure, one skilled in the art would clearly not know what is the specific utility of the instant PRO4380 with respect to glucose or FFA uptake. The specification (p. 166) discloses that a protein is scored as a 'positive' in the glucose and FFA uptake assay if any one of four conditions is met:

a) Glucose uptake decreases by at least 50% from control

b) Glucose uptake increases to at least 150% of control

c) FFA uptake decreases by at least 50% from control

d) FFA uptake increases to at least 150% of control

But the specification does not indicate which of the above-listed conditions applies to PRO4380. Is it stimulation or inhibition of glucose uptake? Would PRO4380 polypeptides be useful to treat

hyper-insulinemia or hypo-insulinemia, two opposite conditions? Or would it be useful in stimulating or inhibiting glucose uptake?

Furthermore, the observed differences do not appear to be statistically significant and the cutoff points appear to be arbitrary and there is not obvious scientific basis for them. For example, Santomauro et al. (1999. Diabetes 48:1836-1841) teach that 56.5% decreases in FFA levels are statistically significant and correlated with physiological improvements, but it is not clear from either the prior art or the specification whether 50% decreases are useful (see Table 2 from Santomauro et al.). Note that 50% decreases in *plasma* insulin do appear to be significant, but it is not clear whether this is due to a doubling of insulin uptake by skeletal muscle or by other tissues, or whether it is due to changes in the amount of insulin production. Similarly, the observation that 56.5% decreases in *circulating* FFAs is significant and correlated with physiological improvements does not indicate that a doubling of uptake of FFAs *by skeletal muscle cells* will lead to the same decreases in FFAs. For example, doubling the amount of FFA uptake from 1% to 2% of total circulating FFAs would not be expected to lead to a 56% decrease in circulating FFA levels. It is unclear to the examiner why one would want to decrease FFA uptake, as that would be expected to result in higher circulating FFAs, which can lead to diabetes (see Santomauro et al., p. 1836, second column, last sentence of first paragraph). Additionally Boden (2003. Exp Clin Endocrinol Diabetes 111:121-124) teaches that increasing plasma FFA leads to atherosclerosis (p. 123, first column, under Summary). Additionally, it is not clear from either the prior art or the post-filing art that FFA uptake is a useful assay. Boden teaches that there is not a cause and effect relationship between FFA-mediated changes in intramyocellular triglyceride content and changes in insulin resistance (p. 122, first column, in the middle of the first full paragraph). Kelley et al. (1999. Am J Physiol 277 (Endocrinol Metab 40):E1130-E1141) teach that free fatty acid uptake may not be as important in determining obesity as other factors, such as fatty acid oxidation (see p. E1139, second column first full paragraph).

35 USC § 101 specifically requires that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. Because the instant specification, as filed, fails to disclose a specific role of PRO4380 in glucose and/or FFA uptake, one would have reasons to conclude that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form.

The data presented in Example 41 (p. 168 – 169) of the specification indicate that PRO4380 was positive in the Mouse Kidney Mesangial Cell Proliferation Assay. It is acknowledged that proliferation of mammalian kidney mesangial cells is useful for the repair of kidneys following damage. However, the threshold used in determining whether a particular PRO molecule counts as "positive" in this assay would not be considered reasonable by one of skill in the art. The specification discloses (p. 169, lines 1 – 2) that positives in this assay include anything which is at least 15% over the control reading. The post-filing publication by Rovin et al. (2002. Kidney International 61:1293-1302) indicates that a 21% increase in human mesangial cell proliferation is not statistically significant (see particularly p. 1296, lines 3 – 6). Note that the assay used by Rovin et al. is similar to that disclosed in Example 41: both used the Cell-Titer 96 reagent from Promega, measured absorbance at 490 nm, and expressed the results as the ratio of the absorbance for a given treatment to that of control cells (see Specification, p. 168 – 169, and Rovin et al., p. 1294, second column, second complete paragraph). Because the specification does not disclose the degree to which PRO4380 increased cell proliferation, or whether or not the results were statistically significant, the teachings of Rovin et al. indicate that PRO4380 is not useful in the proliferation of kidney mesangial cells. Clearly, further research and experimentation are required to find out whether the PRO4380 is useful as asserted.

A substantial utility, *by definition*, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In the instant case, the mere fact that PRO4380 was "positive" in two assays is at the most, an interesting invitation for further research, experimentation and confirmation as to whether the PRO4380 is useful as a treatment for hyper-insulinemia, hypo-insulinemia, or kidney mesangial cell proliferation. The further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the claimed invention is not considered specific or substantial.

Claims 22 - 27 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 – 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 states that the claimed antibody "binds" the protein of SEQ ID NO:57, whereas dependent claim 27 states that the antibody "specifically binds". The term "specifically" in claim 27 is a relative term that renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Further the use of the term in the dependent claim raises the issue that the antibodies of the other claims may not be specific to the protein, in which case the metes and bounds of the claims are in question.

Claim 25 is further indefinite as an antibody cannot be a fragment of itself.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 22 – 25 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben et al (WO 99/58660, published 18 November 1999, pp. 48 – 50, 195 – 197, and 81 – 82 of the sequence listing), as evidenced by Harlow et al. (1988. Antibodies: A Laboratory Manual). Ruben et al. teach a sequence, SEQ ID NO:131, which is 99.6% identical to SEQ ID NO:57 of the instant application. Ruben et al. teach specific preferred epitopes along the entire length of the protein which can be used for the production of antibodies (see p. 49, lines 17 – 20). Ruben et al. further teach that their antibodies include monoclonal antibodies, Fab and F(ab')2 fragments, chimeric, single-chain, and humanized antibodies (see paragraph spanning pp. 196 – 197). Although the polypeptide sequence of Ruben et al. is not identical to that of SEQ ID NO:57, the two are so close that it is expected that an antibody raised against either one would recognize the other. The teachings of Harlow et al. are particularly informative.

Page 76 of Harlow indicates that long peptides, including the hydrophilic regions, are likely to produce antibodies and that sequences as short as six amino acid residues can be immunogenic. Clearly the high degree of identity between the two peptide sequences, and the fact that the hydrophobic region identified by applicant as the transmembrane domain is identical in both, indicates that the antibodies produced by Ruben et al. will recognize the polypeptide of SEQ ID NO:57. The prior art teachings of Ruben et al. therefore meet the limitations of claims 22 – 25 and 27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruben et al., in view of Holmes et al (1995. Current Protocols in Immunology, pp. 5.35 – 5.3.8). The claim is drawn to a labeled antibody which binds to SEQ ID NO:57. Ruben et al. teach antibodies which bind to SEQ ID NO:57. Ruben et al. do not teach a labeled antibody. Holmes et al. teach conjugation of multiple labels (FITC, biotin, Texas Red, and phycobilipoproteins) to antibodies for detection. It would have been obvious to one of ordinary skill in the art to label the antibodies of Ruben et al. for purposes of detecting PRO4380, using one of the protocols provided by Holmes et al., with a reasonable expectation of success. A motivation for doing so would be to label a cell or cells that express PRO4380, and Holmes teaches preferred methods for labeling as recognized the skilled artisan.

Conclusion

No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
March 4, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
3-7-05